UNIVESIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

MARINA DA SILVA

IMPACTO DA IDADE E DAS MODALIDADES DE TRATAMENTO NAS TAXAS DE SOBREVIDA EM PACIENTES COM CARCINOMA DE CÉLULAS ESCAMOSAS ORAL

IMPACT OF AGE AND TREATMENT MODALITIES ON SURVIVAL RATES IN PATIENTS WITH ORAL SQUAMOUS CELL CARCINOMA

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Dissertação apresentada à faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para obtenção do título de mestra em Estomatopatologia, na área de Estomatologia.

Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Master in Oral Medicine and Oral Pathology, in the Stomatology area.

Orientador: Prof. Dr. Luiz Paulo Kowalski
Coorientador: Prof. Dr. Alan Roger dos Santos Silva

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RESUMO

O carcinoma de células escamosas (CCE) oral é a neoplasia maligna mais comum em cabeça e pescoço. Atualmente, a cirurgia é o principal tratamento para o CCE oral, frequentemente associada a terapias adjuvantes para pacientes com fatores prognósticos desfavoráveis. O impacto do tratamento e da idade nos resultados de sobrevida dos pacientes jovens é um tema ainda em debate. Alguns estudos não revelam diferenças significativas na sobrevida entre pacientes jovens e mais velhos, enquanto outros sugerem um prognóstico menos favorável para os jovens. O objetivo deste estudo foi avaliar a relação entre a idade dos pacientes, as modalidades de tratamento e as taxas de sobrevida no CCE oral, analisando dados do Registro Hospitalar de Câncer (RHC) da Fundação Oncocentro de São Paulo (FOSP). Foram incluídos pacientes com diagnóstico histopatológico de CCE oral entre 2000 e 2020. Os sítios anatômicos (C02, C03, C04, C05, exceto C05.1-C05.2, e C06) e os tipos morfológicos (8051, 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8083 e 8084) foram definidos de acordo com a Classificação Internacional de Doenças para Oncologia (CID-O-3). As análises estatísticas, incluindo taxas de sobrevida e modelos de regressão de Cox, foram realizadas com o programa R. Um total de 15.747 casos de CCE oral foram identificados, dos quais 15.056 (95,6%) correspondem a pacientes com idade >40 anos (mais velhos) e 691 (4,3%) a pacientes com idade ≤40 anos (jovens). A média de idade foi de 59,5 anos, e o sexo masculino predominou em ambos os grupos. A maioria dos pacientes foram submetidos à cirurgia isolada, observada em 31% dos jovens e 24% dos mais velhos. Outras modalidades de tratamento frequentes incluíram cirurgia combinada com radioterapia (RT) e cirurgia combinada com quimiorradioterapia (CTRT). O tempo médio entre o diagnóstico e o início do tratamento foi de 45 dias para os pacientes jovens e 60 dias para os pacientes mais velhos. Aproximadamente 50% dos pacientes mais velhos iniciaram o tratamento após 60 dias, em comparação com 38% dos pacientes jovens. A taxa de sobrevida global (SG) em 5 anos foi de 45,2% para os jovens e 32% para os pacientes mais velhos. Entre as modalidades de tratamento, a SG foi superior para os jovens submetidos à cirurgia isolada, com uma taxa de 75,6%, enquanto para os pacientes mais velhos foi de aproximadamente 52,7%. Nas outras modalidades que envolveram cirurgia, a SG também foi mais alta entre os jovens. Em relação ao risco de mortalidade, os pacientes mais velhos apresentaram um risco aumentado em comparação com os jovens, particularmente quando tratados com cirurgia isolada, cirurgia combinada com RT e cirurgia combinada com CTRT. Conclui-se que a cirurgia isolada foi a modalidade de tratamento mais comum tanto para jovens quanto para pacientes mais velhos. As taxas de SG foram mais altas para os jovens submetidos à cirurgia isolada, enquanto os pacientes mais velhos mostraram um risco maior de mortalidade quando tratados com cirurgia isolada, cirurgia combinada com radioterapia e cirurgia combinada com quimiorradioterapia, em comparação com os pacientes mais jovens.

Palavras-chave: câncer de cabeça e pescoço, grupos etários, adulto jovem, prognóstico, sobrevida

ABSTRACT

Oral squamous cell carcinoma (OSCC) is the most common malignant neoplasm in the head and neck region. Currently, surgery is the primary treatment for OSCC, often combined with adjuvant therapies for patients with unfavorable prognostic factors. The impact of treatment and age on survival outcomes for younger patients remains a topic of ongoing debate. Some studies show no significant differences in survival between younger and older patients, while others suggest a less favorable prognosis for younger individuals. This study aimed to assess the relationship between patient age, treatment modalities, and survival rates in OSCC by analyzing data from the São Paulo State Hospital-Based Cancer Registry (Oncocentro Foundation – FOSP). The study included patients with histopathological diagnoses of OSCC from 2000 to 2020. Anatomical sites (C02, C03, C04, C05 excluding C05.1-C05.2, and C06) and morphological types (8051, 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8083, and 8084) were defined according to the International Classification of Diseases for Oncology (ICD-O-3). Statistical analyses, including survival rates and Cox regression models, were conducted using R software. A total of 15,747 cases of OSCC were identified, with 15,056 (95.6%) being patients older than 40 years (older patients) and 691 (4.4%) being patients aged 40 years or younger (younger patients). The mean age was 59.5 years, and the male gender predominated in both groups. The majority of patients underwent surgery alone, observed in 31% of younger patients and 24% of older patients. Other frequently used treatment modalities included surgery combined with radiotherapy (RT) and surgery combined with chemoradiotherapy (CTRT). The average time between diagnosis and the initiation of treatment was 45 days for younger patients and 60 days for older patients. Approximately 50% of older patients began treatment after 60 days, compared to 38% of younger patients. The five-year overall survival (OS) rate was 45.2% for younger patients and 32% for older patients. Among treatment modalities, OS was higher for younger patients undergoing surgery alone, with a rate of 75.6%, compared to approximately 52.7% for older patients. For other surgical modalities, OS rates were also higher among younger patients. Regarding mortality risk, older patients exhibited an increased risk compared to younger patients, particularly when treated with surgery alone, surgery combined with RT, and surgery combined with CTRT. It can be concluded that surgery alone was the most common treatment modality for both younger and older patients. Survival rates were higher for younger patients undergoing surgery alone, while older patients showed a higher mortality risk when treated with surgery alone, surgery combined with radiotherapy, and surgery combined with chemoradiotherapy compared to younger patients.

Key-words: cancer of head and neck, age groups, young adult, prognosis, survival

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1. INTRODUÇÃO

O câncer em boca é um grupo de neoplasias malignas que afetam diferentes áreas anatômicas na região da cabeça e do pescoço (INCA, 2022). O carcinoma de células escamosas (CCE) é o tipo mais comum de câncer de boca, sendo responsável por 90% de todos os tumores malignos da boca. Este se origina do epitélio de revestimento da cavidade oral e pode acometer qualquer região da boca, sendo a borda lateral de língua a mais frequente, seguido pelo assoalho de boca (Kaminagakura et al., 2022). Na literatura internacional, não há uma padronização das localizações primárias incluídas nas definições de câncer de cavidade oral ou câncer de boca (INCA, 2022). Dessa forma, neste estudo, não consideramos como parte da cavidade oral lábios e orofaringe, uma vez que estes apresentam fatores de risco distintos, como a exposição à radiação solar e a infecção por HPV, respectivamente. Em 2022, o câncer de lábios e cavidade oral ocupou a décima sexta posição entre os tipos de câncer mais prevalentes, com 389.485 novos casos e 188.230 óbitos (Bray et al., 2024). Segundo o Instituto Nacional de Câncer (INCA), para o Brasil, o número estimado de casos novos de câncer da cavidade oral é de 15.100 para cada ano do triênio de 2023 a 2025, com um risco estimado de 6,99 por 100 mil habitantes (INCA, 2023).

Entre os principais fatores de risco para o desenvolvimento de CCE oral estão o consumo de álcool e tabaco. O hábito de mastigar folhas de Betel e noz de areca com ou sem tabaco também é um fator de risco para o câncer de boca, contudo é mais prevalente em países do sul e leste da Ásia e na Melanésia (Warnakulasuriya e Greenspan, 2020). O HPV geralmente não está associado ao CCE oral ao contrário do CCE de orofaringe (Kaminagakura et al., 2022). O perfil mais característico do CCE oral inclui homens na sexta década de vida, especialmente os que consomem álcool e tabaco (Warnakulasuriya e Greenspan, 2020). No entanto, casos em pacientes jovens, não usuários de álcool e tabaco, têm se tornado mais frequentes nos últimos anos (Llewellyn et al., 2003; Toporcov et al., 2015). O aumento na incidência de CCE oral em pacientes jovens tem sido observado no mundo todo, sendo a língua o local mais frequentemente afetado (Lee et al., 2021; Warnakulasuriya e Greenspan, 2020).

O diagnóstico ocorre através da identificação de alterações teciduais durante o exame clínico, seguido de confirmação por biópsia e análise histopatológica. As lesões costumam ser assintomáticas nos estágios iniciais, mas podem causar dor à medida que a doença progride e afeta estruturas adjacentes (INCA, 2022). No momento do diagnóstico é comum observar cânceres em estágios avançados em grande parte dos casos (Kaminagakura et al., 2022; INCA, 2022). Em pessoas mais jovens, esse atraso pode ser maior, pois os profissionais da atenção primária não suspeitam de câncer (Warnakulasuriya, 2009).

O atraso entre o diagnóstico e o início do tratamento pode levar a piores resultados de sobrevida devido à progressão do estadiamento (Kowalski e Carvalho, 2001; Murphy et al., 2016). O prognóstico do CCE oral está fortemente ligado ao estadiamento da doença no momento do diagnóstico. Quanto mais avançada a doença, pior é o prognóstico, e menores são as taxas de sobrevida dos pacientes. No Brasil, mais de dois terços dos casos são diagnosticados em estágios avançados, resultando em baixas taxas de sobrevida, que giram em torno de 50% em cinco anos (INCA, 2022).

A National Comprehensive Cancer Centers Network (NCCN) emite diretrizes baseadas em evidências e em opiniões de especialistas para o tratamento do câncer nos Estados Unidos, além disso é considerada por muitos como o padrão ouro para o tratamento do câncer (Cohen et al., 2022). Os desafios para a adesão às diretrizes da NCCN persistem devido a vários fatores, como disponibilidade de tratamento, julgamento clínico, idade do paciente, preferências, crenças e autonomia. A não adesão está associada à diminuição da sobrevida geral, independentemente do motivo (Cohen et al., 2022). No Brasil, há a Sociedade Brasileira de Oncologia Cínica (SBOC), que emite anualmente guias de orientação de conduta atualizados, que consideram a realidade brasileira, com objetivo de oferecer uma referência aos especialistas no tratamento dos pacientes oncológicos (SBOC, 2024).

Estudos focados em CCE de língua indicam que adultos jovens tendem a apresentar doenças mais agressivas e exibir piores resultados de sobrevida, o que leva à recomendação de tratamentos agressivos para este grupo (Kaminagakura et al., 2022; Oliver et al., 2019). No entanto, outros estudos mostraram resultados mais favoráveis em pacientes jovens, questionando a justificativa de tomar decisões terapêuticas baseadas unicamente na idade (Oliver et al., 2019). Um estudo sobre CCE oral em pacientes idosos destacam uma baixa taxa de sobrevida relacionada, em parte, às maiores complicações enfrentadas por esse grupo, tornando-os mais suscetíveis a infecções e consequentemente mais propensos a falecer prematuramente (Yamada et al., 2020). Além disso, os idosos frequentemente experimentam mais reações adversas aos medicamentos devido ao processo natural de envelhecimento, o que sugere a necessidade de abordagens de tratamento diferenciadas entre jovens e idosos (Yamada et al., 2020).

Atualmente, a cirurgia é o principal tratamento para o CCE oral, frequentemente combinada com terapias adjuvantes para pacientes com fatores prognósticos adversos, como invasão perineural, envolvimento linfonodal e extensão extranodal (Mesia et al., 2021; Köhler et al., 2022; SBOC, 2023; NCCN, 2024). As modalidades de tratamento podem variar conforme a idade, uma vez que estudos prévios sugerem que pacientes mais jovens têm tendência em

receber tratamento trimodal (Oliver et al., 2019; Yang et al., 2023), enquanto outros estudos referem que pacientes mais velhos tendem a receber menos radioterapia (Xu et al., 2019). O impacto do tratamento e da idade nos resultados de sobrevida em pacientes jovens é um tema ainda em debate. Alguns estudos não demonstram diferenças significativas nos resultados de sobrevida entre pacientes mais jovens e mais velhos (Kaminagakura et al., 2022; Blanchard et al., 2017; Kaminagakura et al., 2010), enquanto outros apontam um prognóstico menos favorável entre os pacientes jovens (Ferreira et al., 2021; Mneimneh et al., 2021).

Diante do exposto, o propósito deste trabalho é explorar a relação entre a idade do paciente, o tratamento administrado e as taxas de sobrevida geral no CCE oral, por meio da análise de dados provenientes do Registro Hospitalar de Câncer da FOSP.

2. ARTIGO

Age-Stratified Treatment and Survival Analysis in Oral Squamous Cell Carcinoma Patients Based on Hospital-Based Cancer Registry

Artigo submetido ao periódico *Oral Oncology* (Anexo 3)

Marina da Silva[a]*, Maria Paula Curado[b], Hugo Fontan Köhler[c], Alexandre Bezerra[d], Alan Roger Santos-Silva[a], Luiz Paulo Kowalski[c,d]

Affiliation

[a] Diagnosis Department, Semiology and Oral Pathology Areas, Piracicaba Dental School, State University of Campinas (UNICAMP), 13414-903, Piracicaba, SP, Brazil.

[b] Group of Epidemiology and Statistics on Cancer, International Research Center, A.C. Camargo Cancer Center, 01509-010, São Paulo, SP, Brazil.

[c] Department of Head and Neck Surgery and Otorhinolaryngology, A.C. Camargo Cancer Center, 01509-010, São Paulo, SP, Brazil.

[d] Department of Head and Neck Surgery, University of São Paulo Medical School, 01246-000, São Paulo, SP, Brazil.

Corresponding author

Marina da Silva

Department of Oral Diagnosis

Piracicaba Dental School, State University of Campinas (UNICAMP)

Av. Limeira, 901, Areião,13414-903, Piracicaba, SP, Brazil

Phone number: +55 42 99917-5930

E-mail: marinasilvapg@gmail.com

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ABSTRACT

Background: The impact of treatment and age on survival outcomes in young patients continues to be a topic of discussion.

Objectives: The aim of this study was to assess the relationship between patient age, treatment delivered, and survival outcomes in Oral Squamous Cell Carcinoma (OSCC) utilizing data from the São Paulo State Hospital-Based Cancer Registry (Oncocentro Foundation – FOSP).

Methods: All OSCC cases registered in the FOSP database from 2000 to 2020 were included in the study. Overall survival (OS) rates were analyzed using the Kaplan-Meier method to assess survival probabilities. Cox multivariate regression analysis and corresponding 95% confidence intervals (CI) were employed to determine the impact of covariates on survival.

Results: A total of 15,747 OSCC cases were identified, with 691 (4.3%) falling into the under 40 years age group (young patients). Surgical intervention as a single-treatment modality was predominant, accounting for treatments in 31% of the younger cohort, compared to 24% in patients over 40 years of age (older patients). The 5-year OS stratified by age groups was considerably higher in the younger cohort (45.2% vs 32%), particularly among those who underwent surgical interventions (75.6% vs 52.7%).

Conclusion: Younger OSCC patients who underwent surgical treatments experienced improved survival outcomes. Conversely, older patients had an elevated mortality risk across various treatment modalities, including surgery alone, surgery combined with radiotherapy and surgery combined with chemoradiotherapy in relation to their younger counterparts.

Key words: head and neck cancer, age group, young adult, prognosis, survival, treatment.

Introduction

In the head and neck region, the most prevalent cancer originates from the oral cavity, where more than 90% of cases a squamous cell carcinoma [1]. In 2022, lip and oral cavity cancer affected approximately 389,846 individuals worldwide, with 188,438 reported deaths. Among these, 19,301 new cases and 8,343 deaths were registered in Latin America and the Caribbean, while Brazil accounted for 11,029 new cases and 4,700 deaths. Globally, lip and oral cavity cancer rank 16th in incidence and 15th in mortality [2-3].

Surgery is the primary treatment modality for OSCC, often combined with adjuvant therapies for patients with adverse prognostic factors, such as perineural infiltration, lymph node metastases and extranodal extension [4-5]. The impact of treatment and age on survival outcomes in young patients remains a subject of debate. While some studies suggest no significant differences in overall survival and disease-free survival between younger and older patients [6-7], others indicate a less favorable prognosis among young patients [8,9].

This study aims to explore the relationship between patient age, treatment modalities, and survival rates in OSCC by analyzing data retrieved from the FOSP Hospital-Based Cancer Registry. The FOSP is responsible for the coordination, validation, and dissemination of the Cancer Hospital Registries for the State of São Paulo, which is the most developed state in Brazil. The FOSP maintains a reliable database and serves as a model for other databases in Brazil; therefore, we chose to use this database for the present study.

Methods

Study design and patient population

This retrospective cross-sectional study utilized secondary data from the FOSP Hospital-Based Cancer Registry. Since this database is non-nominal and publicly available, ethical approval from a research ethics committee was not required. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was employed to enhance the study's presentation and transparency [10].

Participants

Individuals with histopathologic diagnosis of OSCC registered between January 2000 and December 2020 were included. Anatomical sites defined by the International Classification of Diseases for Oncology (ICD-03) [11], included: C02 except (C02.4), C03, C04, C05 except (C05.1-C05.2), and C06. The anatomical sites C00 and C10, which correspond to the lips and oropharynx, respectively, were not included, as they present distinct risk factors such as solar

radiation exposure and HPV infection, respectively. The histological subtypes of squamous cell carcinoma included were 8051, 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8083, and 8084. Due to the almost complete predominance of conventional squamous cell and the small proportion of other subtypes, the inclusion of these subtypes does not compromise the overall analysis of the sample.

Variables

Collected variables encompassed age groups ('younger' ≤40 years, 'older' >40 years), gender (male and female), clinical stage (TNM: I, II, III and IV), regional metastasis (present: N1, N2, N3 or absent: N0), distant metastasis (present: M1 or absent: M0), topographies (tongue, floor of mouth, gingiva/retromolar trigone, buccal mucosa/vestibule of mouth, palate, multiple locations), treatment modalities (surgery alone, surgery and radiotherapy (RT), surgery and chemoradiotherapy (CTRT), surgery and chemotherapy (CT), CTRT, RT alone, CT alone, other treatments and no treatment), as well as the time elapsed between diagnosis and initiation of treatment (≤60 days, >60 days and the mean duration). The sample selection was based on convenience.

Statistical analysis

Absolute and relative frequencies were calculated. Overall survival (OS) was determined from the date of diagnosis to the date of death (from any cause). For the covariable 'time between diagnostic and treatment initiation' (TDTI), survival was assessed from the treatment initiation date to the date of death from any cause. Statistical analyses were performed using software version 4.3.3 R Core Team (2024) [12], and significance was set at p-value ≤ 0.05. Qualitative variables were analyzed using Fisher exact test. Kaplan-Meier survival curves were plotted, and. cases with missing data were excluded. Survival rates differences were evaluated using the log-rank test. Cox regression models, with 95% confidence intervals (CI) were utilized, including variables deemed with p-value < 0.05 significance on univariate analysis were entered into the multivariable regression model.

Results

Clinical and demographic characteristics

A total of 15,747 cases of OSCC were identified between January 2000 and December 2020. The age range of patients was from 10 to 100 years, with a mean age of 59.5 years. The average age of younger patients was 33.8 years, while that of older patients was 60.7 years.

Among these cases, four patients were aged 10-15, and two were aged 16-18. Age distribution showed 15,056 (95.6%) cases in older patients and 691 (4.3%) in younger patients. Among older patients, males represented 11,839 cases (79%, ratio 3.6:1) while among younger patients, males accounted for 506 cases (73%, ratio 2.7:1).

The most commonly affected site in both age groups was the oral tongue, with 6,593 cases (44%) in older patients and 427 cases (62%) in younger patients, followed by the floor of the mouth. Stages III and IV were predominant at diagnosis, with 10,841 cases (72%) in older patients and 436 cases (63%) in younger patients. Regional metastasis was present in 347 cases (50%) of younger patients and 7,850 (52.8%) of older patients, while distant metastasis was noted in 15 cases (2.2%) of younger patients and 498 cases (3.3%) of older patients (Table 1).

Treatment modalities

The majority of patients underwent surgery alone, with 31% in the younger age group compared to 24% in the older age group. Other treatment modalities commonly observed in both cohorts included surgery combined with RT, with 15% in younger patients and 17% in older patients, and surgery combined with CTRT, with 18% in younger compared to 13% older patients. The mean interval time between diagnostic and treatment initiation for younger patients was 45 days, with 247 cases (38%) receiving treatment after 60 days. In contrast, the average duration for older patients was notably longer at 60 days, with 6,900 patients (50%) commencing treatment after 60 days post diagnosis (Table 1).

Overall survival

The 5-year OS rate, stratified by age was higher in younger patients 45.2% (95% CI, 41.5%-49.3%) than in older patients 32% (95% CI, 31.2%-32.8%) (Supplementary Figure 1). Furthermore, among younger patients, the 5-year OS rates were also higher for those who underwent surgery alone at 75.6% (95% CI, 69.6%-82.2%), surgery combined with RT at 57.5% (95% CI, 48.3%-68.3%), surgery combined with CTRT at 43.2% (95% CI, 34.9%-53.5%) (Figure 1), CTRT at 11.8% (95% CI, 6.7%-20.6%) and other treatments at 19% (95% CI, 12.3%-29.1%) (Figure 2). On the contrary, older patients who underwent surgery alone had a 5-year OS rate of 52.7% (95% CI, 51%-54.5%), surgery combined with RT was at 46.8% (95% CI, 44.8%-48.9%), surgery combined with CTRT at 35.3% (95% CI, 33.1%-37.6%) (Figure 1), CTRT at 17.2% (95% CI, 15.8%-18.8%) and other treatments at 16.8% (95% CI, 15.4%-18.3%) (Figure 2). The 5-year OS for all age groups was 32.5% (95% CI, 31.7%-33.3%) (Supplementary Figure 2). The 5-year OS by TDTI in 0-60 days was 47.3% (95% CI, 42.4%-

52.8%) in younger patients and 34.5% (95% CI, 33.4%-35.7%) in older patients. The TDTI over 60 days in younger patients was 46.5% (95% CI, 40.3%-53.7%) and 32.8% in older patients (95% CI, 31.6%-34%) (Supplementary Figure 3).

Impact of Treatment Modalities on Survival Outcomes

In Table 2, the analyses conducted for the populations aged ≤40 years and >40 years, respectively. In the multivariate analysis for older patients, the treatment modalities CTRT (HR: 1.41; 95% CI, 1.32-1.51; p-value <0.001) and other treatments (HR: 1.89; 95% CI, 1.78-2.01; p-value <0.001) demonstrated an increased risk of death, while surgery combined with RT (Hazard ratio (HR): 0.80; 95% CI 0.74-0.85; p-value <0.001) and surgery combined with CTRT (HR: 0.84; 95% CI, 0.78-0.90; p-value <0.001) showed a reduction in the risk of death compared to patients who underwent surgery alone. Conversely, younger patients exhibited an elevated risk of death across the treatment modalities CTRT (HR: 2.62; 95% CI, 1.76-3.92; p-value <0.001) and other treatment (HR: 3.41; 95% CI, 2.34-4.96; p-value <0.001). Regarding surgery combined with RT (0.99; 95% CI, 0.66-1.48; p-value >0.9) and surgery combined with CTRT (HR: 1.02; 95% CI, 0.68-1.52; p-value >0.9), no significant statistical difference was observed.

The multivariate Cox regression analysis for OS indicated that older patients had an increased risk of death (HR: 1.36; 95% CI, 1.22-1.51) when compared to younger patients (Supplementary Table 3). The univariate analyses are available in Supplementary Table 1. Except for patients treated with chemoradiation, older patients had a worse prognosis than younger patients across all other treatment modalities used (Table 3).

A higher risk of death was observed in patients who did not undergo surgery and had a TDTI of >60 days (HR: 1.06; 95% CI, 1.00-1.13; p-value 0.037) compared to <60 days (Table 4). The univariate analyses are available in Supplementary Table 4.

Discussion

The OS varied between age groups based on the treatment modalities utilized. Older patients generally had poorer OS outcomes even when treated with surgery alone, surgery combined with RT, surgery combined with CTRT and other treatments. On the other hand, younger patients exhibited better OS outcomes in all the treatment modalities analyzed, with the exception of CTRT. In comparison to surgery alone (reference), an increased risk of mortality was noted in CTRT and other treatments groups. Conversely, surgery combined with

RT and surgery combined with CTRT were associated with a decrease risk of mortality in older patients.

Surgery is the most commonly utilized treatment for OSCC, with additional adjuvant treatments often prescribed for patients with adverse prognostic factors. Previous studies have indicated a high proportion of young patients undergoing surgery alone compared what was observed in the current study [13-14]. Additionally, Xu et al. reported that patients over 41 years old were more likely to undergo surgery alone [15]. In our study, surgery alone was the predominant treatment modality, with 31% for young patients compared to 24% for older patients. The other most commonly employed treatments were surgery combined with RT and surgery combined with CTRT. Trimodal treatment is often administered in young patients [14-18]. Moreover, Oliver et al. reported that young patients are more likely to undergo trimodal therapy than older patients. The reasons for patients undergoing intensification are unclear, and further studies are necessary to investigate if practitioners are recommending adjuvant CTRT without a clear indication for adding chemotherapy [14]. On the other side, some studies have indicated that older patients, particularly the elderly, receive less radiotherapy for similar tumor characteristics [15,19]. Due to the often-compromised overall health status, many surgeons tend to opt for a conservative treatment approach in older patients [15]. Our study revealed no significant differences between age groups concerning radiotherapy and trimodal treatment in the relative frequencies.

The association between age and survival in OSCC of HNC remains a topic of debate, as several previous studies have indicated that young adults exhibit a higher survival rate [13,14,16,20-23], while other studies have reported similar outcomes across different age groups [6,7,24,25]. However, data from Garavello et al. suggested that the presence of oral tongue SCC in young individuals is an independent predictor of poorer survival [26], and Vargas et al. noted a trend towards fewer young female patients surviving, although these findings were based on limited sample sizes of both young and older patients [27]. Our five-year OS analysis, displayed better outcomes for young patients compared to older patients.

Regarding the risk of mortality, older patients exhibited a higher risk (HR: 1.36; 95% CI, 1.22-1.51), which aligns with findings from other studies. For instance, Chang et al. used patients aged <45 years as a reference group, with those aged 45-65 years showing similar results (HR: 1.18; 95% CI, 1.01-1.38) and those over 65 years having a higher risk (HR: 1.80; 95% CI, 1.45-2.22) [22]. Blanchard et al. who used ≥ 40 years as a reference group, reported a non-significant trend in younger patients (HR: 0.53, 95% CI, 0.26-1.10) [7], as did Kim et al. using ≤40 years as a reference group (HR:0.685; 95% CI, 0.349-1.347) [28]. However, it is

important to note that the sample size was limited, and the analysis focused solely on tongue tumors.

Delaying the initiation of treatment following the initial consultation can lead to tumor progression and clinical staging alterations that impact therapeutic planning, and potentially have an adverse effect on prognosis [29]. The time interval from initial clinical stage to advanced clinical stage can vary from 3.6 to 63.8 months, with a median of 11.3 months [29]. A study involving a sample exceeding 50,000 cases of HNSCC analyzed the effect of prolonged time to treatment initiation on OS. Cox regression analyses on TDTI for the intervals of 61 to 90 days (HR: 1.08; 95% CI, 1.03-1.13) and over 90 days (HR: 1.23; 95% CI, 1.15-1.32) revealed an increased risk of mortality compared to the reference of 0 to 30 days, while the timeframe of 31 to 60 days did not yield statistically significant results [30]. Our study identified that patients experiencing TDTI exceeding 60 days without undergoing surgery had an increased risk of death (HR: 1.06; 95% CI, 1.00-1.13) as opposed to those treated within 60 days. Patient refusal or healthcare system issues were linked to 94.3% of TDTI [27].

In a study by Mukdad et al. that encompassed 16,423 cases of oral tongue squamous cell carcinoma, the variable of surgery was associated with better OS across all age groups analyzed, except for female patients under 40 years of age, whereas older patients (>40 years) exhibited enhanced outcomes with radiotherapy [31]. A study conducted in China with over 33,000 cases of OSCC, demonstrated an increase in survival across all treatment modalities assessed compared to patients who did not receive or had unknown treatment [18]. Our findings indicated that among older patients, in the multivariate analysis, a reduced risk of mortality was noted when patients underwent surgery combined with RT (HR: 0.80; 95% CI, 0.74-0.85) and surgery combined with CTRT (HR: 0.84; 95% CI, 0.78-0.90), while CTRT and other treatments were associated with an increased risk of mortality compared to patients who underwent surgery. Conversely, in younger patients, CTRT and other treatments were associated with increased mortality risk compared to patients who underwent surgery. Kim et al. reported in their study that the treatment modalities comprising surgery combined with RT or CT, and RT/CT led to poorer survival outcomes relative to patients who underwent surgery. However, it is worth noting that the study had a small sample size, was not stratified by age, and only included patients with tongue SCC [28].

Older patients who underwent surgery alone, surgery combined with RT and surgery combined with CTRT exhibited a higher risk of death compared to younger patients. In the study by Chang et al., older patients (≥45 years) who underwent surgery alone had poorer

survival outcomes compared to patients under 45 years of age (HR: 1.52; 95% CI, 1.15-2.01) [22].

This study is limited by its retrospective design and the lack of data on various risk factors, including alcohol consumption, tobacco use, and detection of HPV-positive cases, which, albeit rare, may occur in the oral cavity. Histopathologic grades and comorbidities were also not captured. However, the study benefited from a significant sample size of OSCC patients, with high-quality data obtained from multiple hospitals in São Paulo state, Brazil.

Conclusion

Younger patients who underwent surgery showed superior OS outcomes compared older patients. Additionally, older patients had an increased risk of death when receiving surgery alone, surgery combined with RT and surgery combined with CTRT, in comparison to their younger counterparts. Early diagnosis is crucial, as most patients in both groups were identified at advanced clinical stages. This situation hinders therapeutic planning and consequently affects patient survival. Early detection can significantly improve clinical outcomes by allowing for more effective and timely interventions.

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The funding source exerted no influence on the study design, data collection, analysis, interpretation, manuscript drafting, or the decision to submit the article for publication.

Ethics

The study did not require ethics committee approval because it used a publicly available database without risk of disclosure of participants' data (Resolution 510/16 of the Brazilian National Health Council).

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Table 1 – Clinical and Demographic Characteristics

Characteristic	Age ≤40y n=691	Age >40y n=15,056	p-value
Sex, n (%)			**<0.001**
Female	185 (27%)	3,217 (21%)	
Male	506 (73%)	11,839 (79%)	
Clinical stage, n (%)			**<0.001**
I	131 (19%)	2,030 (13%)	
II	124 (18%)	2,185 (15%)	
III	109 (16%)	2,499 (17%)	
IV	327 (47%)	8,342 (55%)	
Regional metastasis, n (%)			0.3
Absent	344 (50%)	7,138 (47%)	
Present	347 (50%)	7,850 (52,8%)	
Distante metastasis, n (%)			0.12
Absent	676 (98%)	14,558 (97%)	
Present	15 (2.2%)	498 (3.3%)	
Site, n (%)			**<0.001**
Tongue	427 (62%)	6,593 (44%)	
Floor of mouth	104 (15%)	3,370 (22%)	
Gingiva/Retromolar trigone	62 (9.0%)	2,231 (15%)	
Palate	24 (3.5%)	930 (6.2%)	
Buccal mucosa/ Vestibule of mouth	28 (4.1%)	548 (3.6%)	
Multiple locations	46 (6.7%)	1,384 (9.2%)	
Treatment n, (%)			**<0.001**
Surgery alone	212 (31%)	3,619 (24%)	
Surgery + RT	107 (15%)	2,538 (17%)	
Surgery + CTRT	124 (18%)	2,016 (13%)	
Surgery + CT	12 (1.7%)	291 (1.9%)	
CTRT	102 (15%)	2,718 (18%)	
RT	39 (5.6%)	1,400 (9.3%)	
CT	27 (3.9%)	579 (3.8%)	
Other treatments	25 (3.6%)	681 (4.5%)	
No treatment	43 (6.2%)	1,214 (8.1%)	
Time between diagnosis and treatment n, (%)			**<0.001**
≤60 days	401 (62%)	6,933 (50%)	
>60 days	247 (38%)	6,900 (50%)	
Median (days)	45 (19-81)	60 (26-103)	

Abbreviations: ≤40y, younger; >40y, older; RT, radiotherapy; CT, chemotherapy; CTRT, chemoradiotherapy.

Table 2 – Multivariate Cox regression model results by age groups.

Characteristic	Age ≤40y			Age >40y		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Sex (reference: female)						
Male	1.13	0.87-1.47	0.4	1.06	1.01-1.11	**0.028**
Clinical stage (reference: I)						
II	1.72	1.02-2.90	**0.041**	1.32	1.22-1.44	**<0.001**
III	2.69	1.54-4.71	**<0.001**	1.62	1.48-1.78	**<0.001**
IV	4.40	2.52-7.66	**<0.001**	2.42	2.22-2.63	**<0.001**
Regional metastasis (reference: absent)						
Present	1.45	1.04-2.01	**0.027**	1.27	1.20-1.33	**<0.001**
Distante metastasis (reference: absent)						
Present	1.22	0.62-2.41	0.6	1.46	1.32-1.62	**<0.001**
Site (reference: tongue)						
Floor of mouth	0.69	0.51-0.95	**0.024**	0.96	0.91-1.01	0.087
Gingiva/retromolar trigone	1.02	0.72-1.44	>0.9	0.89	0.84-0.94	**<0.001**
Buccal mucosa/vestibule of mouth	1.96	1.18-3.24	**0.009**	1.03	0.93-1.15	0.6
Palate	0.54	0.29-1.04	0.064	0.94	0.86-1.02	0.14
Multiple locations	1.04	0.68-1.59	0.9	1.01	0.94-1.08	0.8
Treatment (reference: surgery alone)						
Surgery + RT	0.99	0.66-1.48	>0.9	0.80	0.74-0.85	**<0.001**
Surgery + CTRT	1.02	0.68-1.52	>0.9	0.84	0.78-0.90	**<0.001**
CTRT	2.62	1.76-3.92	**<0.001**	1.41	1.32-1.51	**<0.001**
Other treatments	3.41	2.34-4.96	**<0.001**	1.89	1.78-2.01	**<0.001**

Abbreviations: ≤40y, younger; >40y, older; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CT, chemotherapy; CTRT, chemoradiotherapy.

Table 3 - Multivariate analysis Cox regression models results by treatment modalities. Multivariate analysis was calculated considering the same covariates included in prior analysis.

Fixed by treatment modalities			
	HR	**95% CI**	**p-value**
Surgery alone			
Age (reference ≤40y)			
>40y	2.37	1.81-3.09	**<0.001**
Surgery + RT			
Age (reference ≤40y)			
>40y	1.67	1.27-2.19	**<0.001**
Surgery + CTRT			
Age (reference ≤40y)			
>40y	1.45	1.14-1.86	**0.003**
CTRT			
Age (reference ≤40y)			
>40y	0.80	0.64-0.99	**0.039**
Other treatments			
Age (reference ≤40y)			
>40y	-	-	-

Abbreviations: ≤40y, younger; >40y, older; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CT, chemotherapy; CTRT, chemoradiotherapy.

Table 4 - Multivariate analysis Cox regression models results by TDTI stratified by age groups, surgery and no surgery. Multivariate analysis was calculated considering the same covariates included in prior analysis.

Fixed by age groups, surgery and no surgery			
	HR	**95% CI**	**p-value**
≤40y			
TDTI (reference: <60 days)	-	-	-
>40y			
TDTI (reference: <60 days)	1.01	0.98-1.06	0.5
Surgery[a]			
TDTI (reference: <60 days)	-	-	-
No Surgery[b]			
TDTI (reference: <60 days)	1.06	1.00-1.13	**0.037**

[a] Patients underwent surgery alone, surgery combined with RT or CT or CTRT.

[b] Patients underwent CTRT, RT alone, CT alone and others treatments.

Abbreviations: TDTI, time between diagnostic and treatment initiation; ≤40y, younger; >40y, older; HR, hazard ratio; CI, confidence interval.

Figure 1 - 5-year OS for patients with OSCC stratified by more common treatment modalities: surgery alone, surgery + RT and surgery + CTRT.

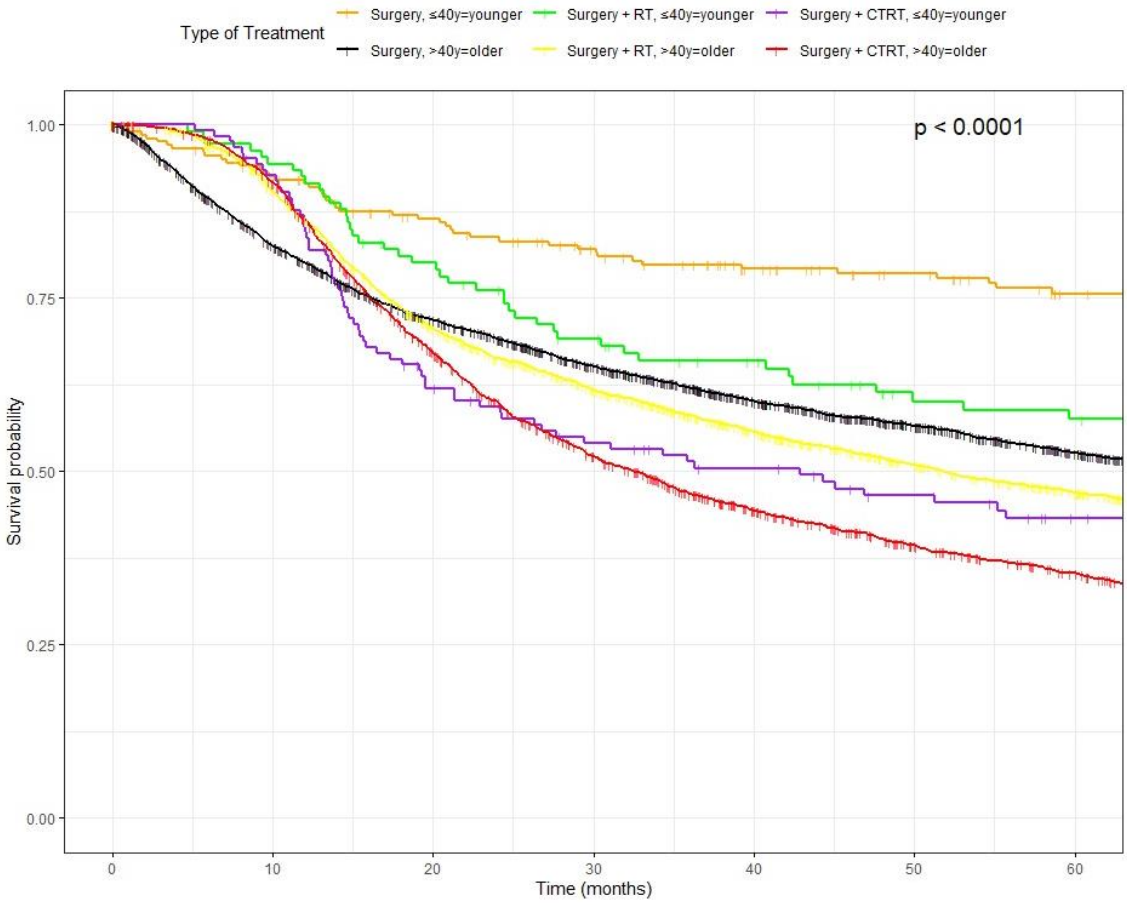
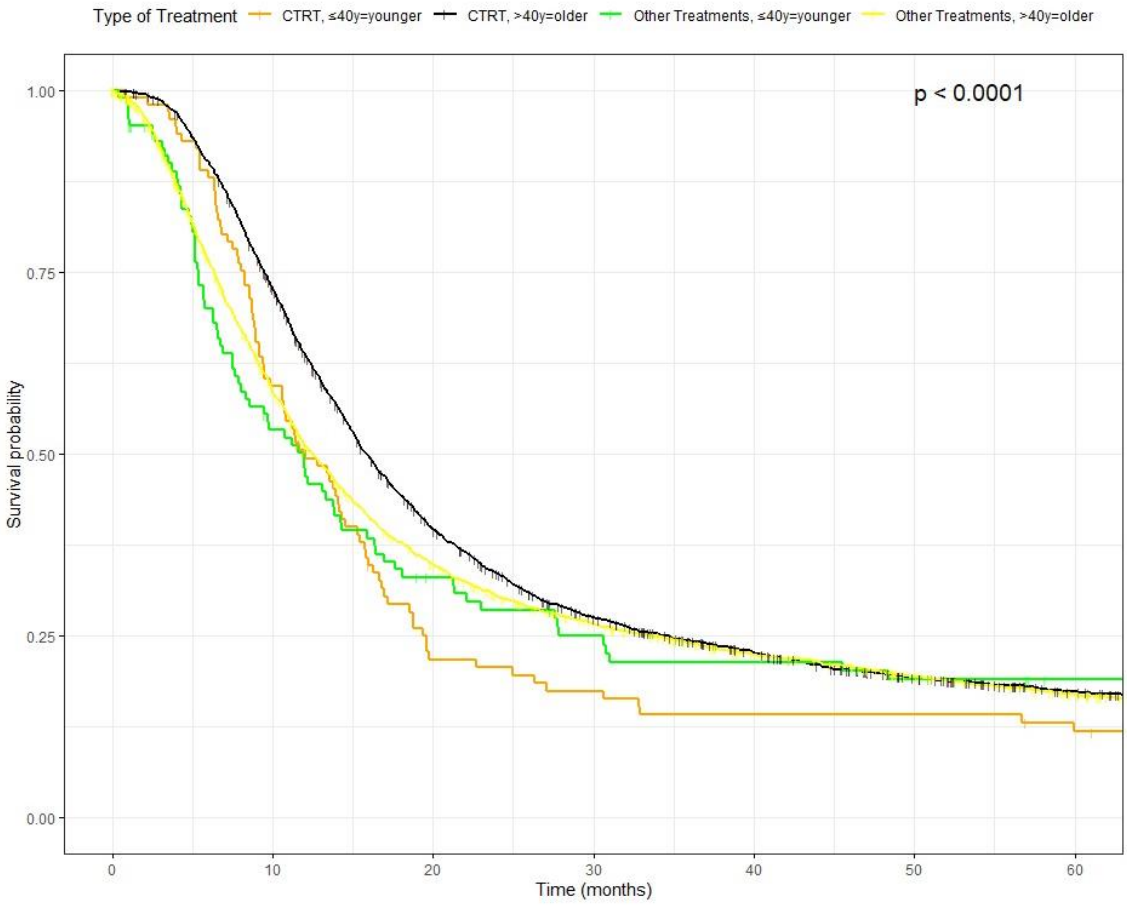


Figure 2 - 5-year OS for patients with OSCC stratified by treatment modalities: CTRT and other treatments.



MATERIAL SUPLEMENTAR DO ARTIGO

Supplementary Table 1 - Univariate analysis Cox regression models results by age groups.

	Age ≤40y			Age >40y		
Characteristic	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Sex (reference: female)						
Male	1.45	1.13-1.88	**0.004**	1.25	1.19-1.31	**<0.001**
Clinical stage (reference: I)						
II	1.76	1.05-2.94	**0.031**	1.31	1.21-1.43	**<0.001**
III	3.59	2.22-5.82	**<0.001**	1.93	1.78-2.09	**<0.001**
IV	7.25	4.72-11.2	**<0.001**	3.10	2.89-3.32	**<0.001**
Regional metastasis (reference: absent)						
Present	3.59	2.85-4.51	**<0.001**	2.04	1.96-2.12	**<0.001**
Distante metastasis (reference: absent)						
Present	2.12	1.09-4.12	**0.026**	2.42	2.19-2.68	**<0.001**
Site (reference: tongue)						
Floor of mouth	1.0	0.73-1.35	>0.9	1.04	0.99-1.09	0.2
Gingiva/retromolar trigone	1.39	0.99-1.95	0.058	0.99	0.93-1.05	0.8
Buccal mucosa/vestibule of mouth	1.37	0.84-2.25	0.2	1.00	0.90-1.12	>0.9
Palate	0.80	0.42-1.51	0.5	1.16	1.07-1.27	>0.9
Multiple locations	1.57	1.04-2.38	**0.033**	1.23	1.15-1.32	**<0.001**
Treatment (reference: surgery alone)						
Surgery + RT	1.91	1.31-2.78	**<0.001**	1.11	1.04-1.18	**0.002**
Surgery + CTRT	2.46	1.73-3.51	**<0.001**	1.39	1.30-1.49	**<0.001**
RT + CT	7.07	5.02-9.96	**<0.001**	2.45	2.30-2.60	**<0.001**
Other Treatments	6.26	4.44-8.83	**<0.001**	2.70	2.54-2.86	**<0.001**

Abbreviations: ≤40y, younger; >40y, older; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CT, chemotherapy; CTRT, chemoradiotherapy.

Supplementary Table 2 - Univariate analysis Cox regression models results by treatment modalities.

Fixed by treatment modalities			
	HR	**95% CI**	**p-value**
Surgery alone			
Age (reference ≤40y)			
>40y	2.71	2.08-3.54	**<0.001**
Surgery + RT			
Age (reference ≤40y)			
>40y	1.61	1.22-2.11	**<0.001**
Surgery + CTRT			
Age (reference ≤40y)			
>40y	1.46	1.15-1.87	**0.002**
RT + CT			
Age (reference ≤40y)			
>40y	0.76	0.61-0.94	**0.011**
Other Treatments			
Age (reference ≤40y)			
>40y	1.06	0.85-1.32	0.6

Abbreviations: ≤40y, younger; >40y, older; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CT, chemotherapy; CTRT, chemoradiotherapy.

Supplementary Table 3 - Univariate and multivariate analysis Cox regression models result by all age groups.

	Univariate			Multivariate		
Characteristic	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age (reference ≤40 y)						
>40y	1.58	1.42-1.76	<0.001	1.36	1.22-1.51	<0.001

Abbreviations: ≤40y, younger; >40y, older; HR, hazard ratio; CI, confidence interval.

Supplementary Table 4 – Univariate analysis Cox regression models results by TDTI stratified by age groups, surgery and no surgery.

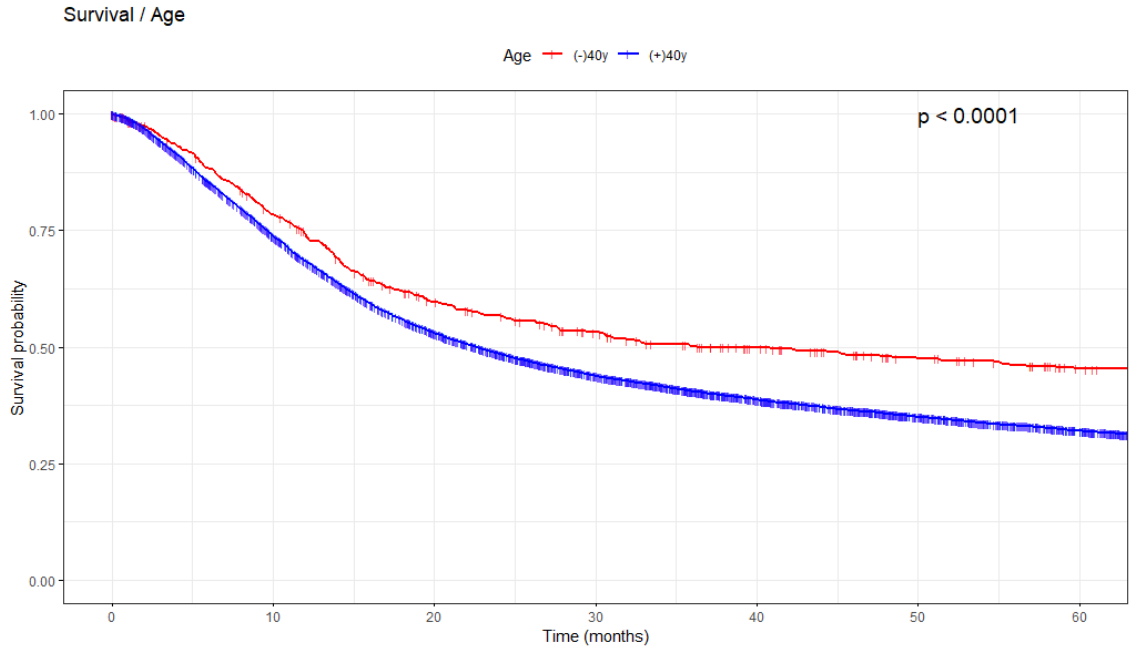
Fixed by age groups, surgery and no surgery			
	HR	**95% CI**	**p-value**
≤40y			
TDTI (reference: <60 days)			
>60 days	1.13	0.91-1.40	0.3
>40y			
TDTI (reference: <60 days)			
>60 days	1.06	1.02-1.11	**0.002**
Surgery[a]			
TDTI (reference: <60 days)			
>60 days	1.00	0.95-1.05	>0.9
No Surgery[b]			
TDTI (reference: <60 days)			
>60 days	1.10	1.04-1.16	**0.001**

[a] Patients underwent surgery alone, surgery combined with RT or CT or CTRT.

[b] Patients underwent RT + CT, RT alone, CT alone and others treatments.

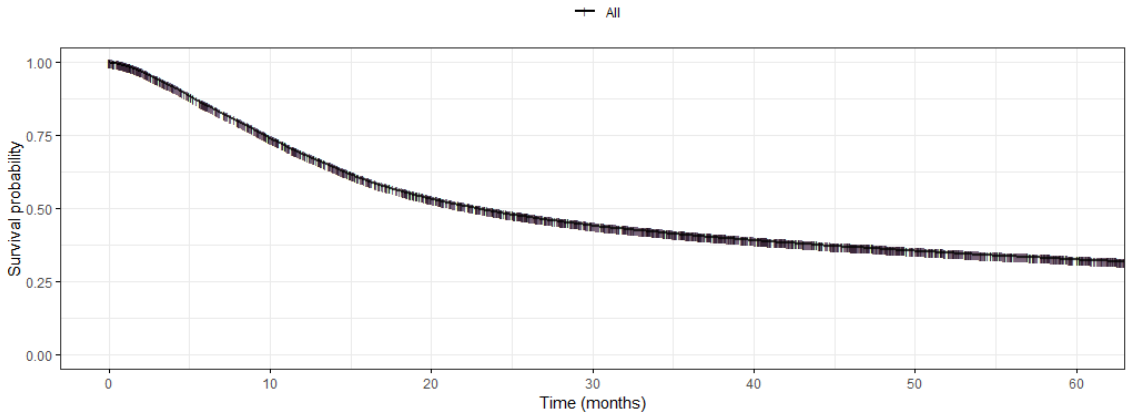
Abbreviations: TDTI, time between diagnostic and treatment initiation; ≤40y, younger; >40y, older; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CT, chemotherapy, CTRT, chemoradiotherapy.

Supplementary Figure 1 – 5-year OS for patients with OSCC stratified by age groups.



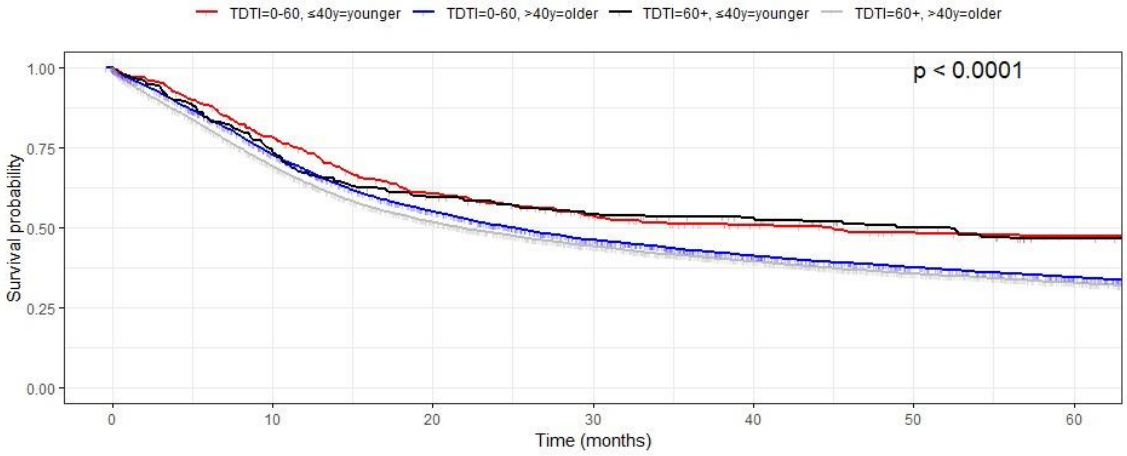
Abbreviations: (-)40y, younger; (+)40y, older.

Supplementary Figure 2 - 5-year OS for patients with OSCC among all age groups.



Abbreviations: All, all age groups.

Supplementary Figure 3 - 5-year OS for patients with OSCC by TDTI in younger and older patients.



3. CONCLUSÃO

- A cirurgia isolada foi a modalidade de tratamento mais comum em ambos grupos etários, jovens e mais velhos;
- A sobrevida geral em cinco anos foi superior em pacientes jovens submetidos à cirurgia isolada em comparação com os pacientes mais velhos;
- Os pacientes mais velhos apresentaram aumento no risco de morte quando tratados com cirurgia isolada, cirurgia combinada com radioterapia e cirurgia combinada com quimiorradioterapia, em relação aos pacientes mais jovens;
- Os pacientes que não foram submetidos à cirurgia e iniciaram o tratamento após 60 dias do diagnóstico apresentaram aumento no risco de morte em comparação com aqueles que iniciaram o tratamento dentro de 60 dias.

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* De acordo com as normas da UNICAMP/FOP, baseadas na padronização do International Committee of Medical Journal Editors – Vancouver Group. Abreviatura dos periódicos em conformidade com o Pubmed.

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ANEXOS

ANEXO 1 - Dispensa de aprovação no Comitê de Ética em Pesquisa

GOVERNO DO ESTADO
DE SÃO PAULO

FUNDAÇÃO ONCOCENTRO DE SÃO PAULO
Secretaria de Estado da Saúde
REGISTRO HOSPITALAR DE CÂNCER

FOSP

DECLARAÇÃO

Declaramos, para os devidos fins, que as bases de dados disponibilizadas no *site* oficial da Fundação Oncocentro de São Paulo - FOSP (https://fosp.saude.sp.gov.br/fosp/diretoria-adjunta-de-informacao-e-epidemiologia/rhc-registro-hospitalar-de-cancer/banco-de-dados-do-rhc/) são de domínio público, não nominais,

Assim, podem ser utilizadas por estudantes, pesquisadores e demais interessados, dispensando aprovação por parte de Comitês de Ética em Pesquisas na realização de projetos, artigos ou outros estudos.

São Paulo, abril de 2024.

Gerência do Registro Hospitalar de Câncer
do estado de São Paulo

R. Oscar Freire, 2396 ▪ São Paulo – SP ▪ CEP 05409-012 ▪ F: (11) 3797-1836 / 3797-1837
http://fosp.saude.sp.gov.br ▪ rhc@fosp.saude.sp.gov.br

ANEXO 2 – Relatório de verificação e prevenção de plágio

Marina_Dissertação.docx

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ANEXO 3 – Comprovante de submissão de artigo

Oral Oncology

Age-Stratified Treatment and Survival Analysis in Oral Squamous Cell Carcinoma Patients Based on Hospital-Based Cancer Registry

--Manuscript Draft--

Manuscript Number:	OO-D-24-1183
Article Type:	Original Research Article
Section/Category:	Epidemiology and Public Health Research
Keywords:	head and neck cancer, age group, young adult, prognosis, survival, treatment
Corresponding Author:	Marina da Silva State University of Campinas BRAZIL
First Author:	Marina da Silva, DDS
Order of Authors:	Marina da Silva, DDS
	Maria Paula Curado, MD, PhD
	Hugo Fontan Köhler, MD
	Alexandre Bezerra, MD, PhD
	Alan Roger Santos-Silva, DDS, PhD
	Luiz Paulo Kowalski, MD, PhD
Abstract:	Background: The impact of treatment and age on survival outcomes in young patients continues to be a topic of discussion. Objectives: The aim of this study was to assess the relationship between patient age, treatment delivered, and survival outcomes in Oral Squamous Cell Carcinoma (OSCC) utilizing data from the São Paulo State Hospital-Based Cancer Registry (Oncocentro Foundation – FOSP). Methods: All OSCC cases registered in the FOSP database from 2000 to 2020 were included in the study. Overall survival (OS) rates were analyzed using the Kaplan-Meier method to assess survival probabilities. Cox multivariate regression analysis and corresponding 95% confidence intervals (CI) were employed to determine the impact of covariates on survival. Results: A total of 15,747 OSCC cases were identified, with 691 (4.3%) falling into the under 40 years age group (young patients). Surgical intervention as a single-treatment modality was predominant, accounting for treatments in 31% of the younger cohort, compared to 24% in patients over 40 years of age (older patients). The 5-year OS stratified by age groups, was considerably higher in the younger cohort (45.2% vs 32%), particularly among those who underwent surgical interventions (75.6% vs 52.7%). Conclusion: Younger OSCC patients who underwent surgical treatments experienced improved survival outcomes. Conversely, older patients had an elevated mortality risk across various treatment modalities, including surgery alone, surgery combined with radiotherapy and surgery combined with chemoradiotherapy in relation to their younger counterparts.